General

Guideline Title

Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Jun. 55 p. (Technology appraisal guidance; no. 344).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Ofatumumab in combination with chlorambucil is recommended as an option for untreated chronic lymphocytic leukaemia only if:

- The person is ineligible for fludarabine-based therapy and
- Bendamustine is not suitable and
- The company provides ofatumumab with the discount agreed in the patient access scheme (PAS)

People whose treatment with ofatumumab is not recommended in this National Institute for Health and Care Excellence (NICE) guidance, but was started within the National Health Service (NHS) before this guidance was published, should be able to continue ofatumumab until they and their NHS clinician consider it appropriate to stop.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Chronic lymphocytic leukaemia

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Hematology

Internal Medicine

Oncology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To evaluate the clinical effectiveness and cost-effectiveness of ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia

Target Population

Patients with untreated chronic lymphocytic leukaemia for whom fludarabine-based therapy is unsuitable

Interventions and Practices Considered

Ofatumumab in combination with chlorambucil or bendamustine

Major Outcomes Considered

- Clinical effectiveness
    - Progression-free survival
    - Overall survival
    - Response rates
    - Adverse effects
    - Health-related quality of life
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by Peninsula Technology Assessment group (PenTAG) (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Description of Manufacturers Search Strategy and Comment on Whether the Search Strategy Was Appropriate

The ERG is content to accept the searches as submitted and including the additional information provided through clarification. The ERG draws the committee's attention to the fact that the literature search for clinical effectiveness was limited to adult only populations. The manufacturer has provided a rationale for this decision. The manufacturer did not provide a search strategy for indirect comparisons. The ERG raised the absence of searches as a question for clarification, and the manufacturer provided a response (see the ERG report).

Randomised Clinical Trials

The manufacturer provided information on the search strategy for clinical effectiveness. The database search strategies (as included in the manufacturer submission) are reproduced in Appendix A of the ERG report. In summary, searches were carried out in the following bibliographic databases:

MEDLINE (PubMed)
MEDLINE In-Process (this content was accessed by using the PubMed interface, which contains the In-Process material)
EMBASE (Dialog for the initial submission. Embase.com was used to update the literature searches)
The Cochrane Library (Wiley interface), including: The Cochrane Database of Systematic Reviews (CDSR), The Cochrane Central Register of Controlled Trials (CENTRAL), and the Database of Abstracts of Reviews of Effectiveness (DARE)
BIOSIS (via ProQuest, formally Dialog)

Additionally, the clinical trials registry, clinicaltrials.gov, was searched.

The following conference proceedings and Web sites were searched:

- American Society of Clinical Oncology
- European Society for Medical Oncology
- American Society of Hematology and its annual meeting

The ERG notes that the British Society for Haematology Annual Meeting conference database was not searched.

The manufacturer limited these conference proceedings searches to the last 2 years. The ERG feels that this is highly restrictive, especially given that the study which forms the basis of this submission, is a conference abstract from 2009.

The searches were initially carried out on 21st August 2012, and an update search was performed on 20th December 2013. Population search terms (chronic lymphocytic leukaemia/leukemia) were combined with intervention search terms (ofatumumab or chlorambucil, as well as other specified comparators, including bendamustine, rituximab or lenalidomide), and an appropriate balance of Medical Subject Headings (MeSH), free-text and supplementary concept terms were used. A variety of synonyms were used to ensure an appropriate balance of sensitivity and specificity. The ERG notes, however, that some alterative names for the intervention were not included in the search (Humax, Humax-CD20, gsk 1841157, gsk1841157 and Humac). The ERG has run brief, supplementary searches, and find that the omission of these terms does not appear to

have impacted on the retrieval. A suitable clinical trials filter was applied to the MEDLINE and EMBASE searches, and the manufacturer applied a randomized controlled trial (RCT) filter to the Cochrane and BIOSIS searches. The initial searches were not limited by publication date and so were run from database inception; the update searches were limited from 1st August 2012 to 20th December 2013.

The ERG is content to accept these searches. However, they note that in the manufacturer's report, all clinical effectiveness searches are limited to adult-only populations. This restriction is not in keeping with the scope and the ERG asked the manufacturer to repeat the searches, removing this restriction. They received the following response: "The searches could be repeated to include the paediatric population, as requested, but this would require additional time. Chronic lymphocytic leukaemia, however, is a disease of the elderly with a median age at diagnosis of 72 years and it is unusual and very rare in children." See the ERG report for more information.

Whilst the ERG understands that the paediatric populations are not, in theory, relevant to the decision problem, this is not explicitly stated in the scope. The ERG cannot, therefore, exclude the possibility that relevant studies have been missed.

Appropriateness of the Inclusion and Exclusion Criteria

The submission included RCTs, non-RCTs, single-arm trials and prospective cohort studies, where the intervention was ofatumumab + chlorambucil, or ofatumumab + bendamustine. Comparators for the clinical effectiveness review are not described in the manufacturer's inclusion criteria (see table below), but are described within the submission and are in line with the Scope (i.e., chlorambucil with or without rituximab, or bendamustine with or without rituximab). No restrictions were placed on language.

Table. Eligibility Criteria

Criteria	Included	Excluded
Study Design	• Randomised, controlled, prospective clinical trials • Non-randomised, controlled clinical trials • Single-arm trials or prospective cohort studies where the intervention is determined by a protocol • Open-label follow-up studies • Systematic reviews and meta-analyses	• Preclinical studies • Phase I studies • Single-arm pilot trials • Prognostic studies • Commentaries and letters (publication type) • Consensus reports • Non-systematic reviews • Cross-sectional studies • Prospective observational studies where the intervention is not determined by a protocol (e.g., phase IV studies) • Retrospective studies (e.g., case-control studies, historical-control studies) • Case series or case cohort studies • Case reports
Population	Patients undergoing first line therapy for CLL (not restricted to populations for which fludarabine is inappropriate) No restrictions on age, gender, race or disease stage.	• Patients undergoing second- or third-line therapy • Patients with other forms of leukaemia, e.g., ALL, AML, CML
Interventions	• Monoclonal antibodies R monotherapy; GA-101 (obinutuzumab or afutuzumab) monotherapy • Chemotherapy agents Clb monotherapy (oral alkylating agent); Benda monotherapy (purine analogue) • Combination of monoclonal antibodies and chemotherapy agents OfatClb; OfatBenda; RClb; RBenda; immunomodulatory drugs; lenalidomide monotherapy	• Ofat monotherapy • Studies that do not investigate one of the interventions of interest in at least one of the arms

Criteria	Included	Excluded
Outcomes[a]	• Efficacy outcomes OS; PFS; response to treatment (OR [CR + nPR + PR], CR, and PR); MRD status • Safety and tolerability outcomes AEs (in particular, haematological and infectious toxicities) • Patient reported outcomes Health-related quality of life (e.g., EORTC QLQ-C30, EQ-5D, EORTC QLQ-CLL16)	None

Key: AEs = adverse events; AML = acute myeloid leukaemia; ALL = acute lymphocytic leukaemia; Benda = bendamustine; Clb = chlorambucil; CLL = chronic lymphocytic leukaemia; CML = chronic myeloid leukaemia; CR = complete response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-CLL16 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Chronic Lymphocytic Leukaemia; EQ-5D EuroQoL Five-dimension; MRD = minimal residual disease; nPR = nodular partial-response; Ofat = ofatumumab; OfatClb = ofatumumab + chlorambucil; OfatBenda = ofatumumab + bendamustine; OR = overall response; OS = overall survival; PFS = progression-free survival; PR = partial response; R = rituximab; RBenda = rituximab + bendamustine; RClb = rituximab + chlorambucil.

[a]Studies were not excluded based on the outcomes at the level 1 screen because outcomes can be difficult to determine from the abstract. Therefore, studies were excluded on the basis of outcomes only after the full text was reviewed at level 2.

It should be noted that the manufacturer's inclusion criteria, as provided in the table above, are broader than would be necessary to identify studies evaluating ofatumumab + chlorambucil or ofatumumab + bendamustine. This was done in order to identify studies that could be useful in an evidence network and in indirect treatment comparisons if possible. As such, the ERG considers that the inclusion and exclusion criteria are appropriate.

The submission also explains the process used in study selection (i.e., that two researchers independently reviewed titles and abstracts and the full-texts of studies, that differences in opinion were resolved through discussion to reach agreement, with a third senior researcher consulted where necessary). The ERG considers these methods to be appropriate.

Relevant Studies Not Included in the Submission

The ERG has not identified any further relevant studies that are not included in the submission. The submission, therefore, appears to contain all relevant studies in this area.

Cost-effectiveness

Manufacturer's Review of Cost-effectiveness Evidence

Search Strategy

The manufacturer provided information on the search strategy. In summary, searches were carried out in the following bibliographic databases:

- MEDLINE (PubMed)
- MEDLINE In-Process (this content was accessed by using the PubMed interface, which contains the In-Process material)
- EMBASE (Dialog for the initial submission. Embase.com was used to update the literature searches)
- The Cochrane Library (Wiley interface) including: The National Health Service's Economic Evaluation Database (NHS EED) and Health Technology Assessment Database (HTA)
- EconLIT (Dialog)
- BIOSIS (Dialog)

The following conference proceedings and Web sites were searched for relevant abstracts:

- International Society for Pharmacoeconomics and Outcomes Research
- Key international health technology assessment Web sites, including National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), the Canadian Agency for Drugs and Technologies in Health (CADTH) and the International Network of

Agencies for Health Technology Assessment (INAHTA)

The ERG notes that the British Society for Haematology Annual Meeting conference proceedings were not searched.

In addition, reference lists of included economic analysis, reviews and health technology assessments were searched for relevant articles. Reference lists of any relevant studies, recent systematic reviews and meta-analyses also were searched for sources.

The searches were run on 24th August 2012 and the update searches on 22nd October 2013. Population search terms (chronic lymphocytic leukaemia/leukemia) were combined with intervention search terms (ofatumumab or chlorambucil, as well as other specified comparators, including bendamustine, rituximab and lenalidomide). An appropriate balance of MeSH, free-text and supplementary concept terms were used in the search strategy. A variety of synonyms were used to ensure an appropriate balance of sensitivity and specificity. The ERG notes, however, that some alterative names for the intervention were not included in the search (Humax, Humax-CD20, gsk 1841157, gsk1841157 and Humac). The ERG has run brief, supplementary searches, and find that the omission of these terms does not appear to have impacted on the retrieval.

The search results were date limited from 1st January 1997 to 22nd October 2013.

See Section 5.1.2.1 of the ERG report for the ERG comment on the search strategy.

Inclusion and Exclusion Criteria Used in the Study Selection

Table. Inclusion and Exclusion Criteria for Systematic Review of Economic Evidence

Criteria	Included	Excluded
Population	People undergoing first line therapy for chronic lymphocytic leukaemia	• Patients undergoing second- or third-line therapy (applied to economic evaluations only) • Patients with other forms of leukaemia, e.g., acute lymphoblastic leukaemia, acute myeloid leukaemia, chronic myelogenous leukaemia)
Interventions of Interest	Ofatumumab + chlorambucil; ofatumumab + bendamustine; chlorambucil monotherapy; bendamustine monotherapy; rituximab monotherapy; rituximab + chlorambucil; rituximab + bendamustine; lenalidomide monotherapy; GA-101 (obinutuzumab or afutuzumab)	• Ofatumumab monotherapy • Economic evaluations that did not include one of the interventions of interest in at least one of the arms
Study Type	Economic analyses, utility studies (including studies where utility weights were mapped from other instruments, e.g., disease-specific patient-reported outcome measures), prospective studies reporting costs or resource utilisation; retrospective studies reporting costs or resource utilisation (e.g., cost-of-illness studies, cross-sectional studies); systematic reviews of economic analyses, utility, resource use, or cost studies	Comments and letters (publication type); consensus reports; non-systematic reviews; articles reporting cost estimates that were not based on data (e.g., commentaries making general reference to cost burden)

The ERG believes the inclusion and exclusion criteria were appropriate to the objective of the cost-effectiveness review.

Number of Source Documents

Clinical Effectiveness

In order to provide details on the flow of studies through the review, the manufacturer's submission provides two flow diagrams (see Figure 2 and Figure 3 in the ERG report [see the "Availability of Companion Documents" field]), one for the original review and another for the update. The submission did not report which studies were excluded but gives reasons for exclusion in Figures 2 and 3. The reasons cited for exclusion are

reasonable and in line with the search strategy. The flowcharts demonstrate that 25 studies were included for data extraction.

Of the 25 studies extracted, only one randomised controlled trial (RCT) (COMPLEMENT 1) and one non-RCT (OMB115991) were identified that provided information on ofatumumab, as a first line therapy for chronic lymphocytic leukaemia.

Cost-effectiveness

- The searches conducted by the manufacturer yielded a combined total of 37 included studies. Figure 21 and Figure 22 in the ERG report show the study flow diagram for the original systematic review and updated systematic review, respectively. Eight publications reported utility weight data and 17 reported resource use and/or cost data. Eleven economic evaluations (reported in 12 publications) were identified in the review. Six abstracts were identified. The manufacturer provided a list of abstracts identified in the submission. None of the studies identified were relevant to the decision problem.
- The manufacturer submitted and economic model.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by Peninsula Technology Assessment group (PenTAG) (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Description and Critique of Manufacturer's Approach to Validity Assessment

COMPLEMENT 1

The manufacturer reports the quality assessment of COMPLEMENT 1 according to the Centre for Reviews and Dissemination (CRD) assessment criteria for risk of bias in randomized controlled trials (RCTs). Other details pertaining to the design and methods of COMPLEMENT 1 are also provided in the submission. A summary of these details are given in Table 13 of the ERG report, alongside the ERG critique.

Single-Arm Study OMB115991

The manufacturer reports the quality assessment of OMB115991 according to the Critical Appraisal Skills Programme (2006). Other details pertaining to the design and methods of OMB115991 are also provided in the submission. A summary of these details are given in Table 14 of the ERG report, alongside the ERG critique.

The ERG thinks it important to highlight that OMB115991 is a single-arm study. The design of single-arm studies makes it difficult to assess and generalise results. Results from non-randomised studies may differ from RCT evidence, and case series design is considered to be the weakest source of clinical effectiveness evidence in the hierarchy of study designs.

Description and Critique of Statistical Approaches Used

COMPLEMENT 1

The primary analysis in this RCT was performed on an intent-to-treat (ITT) population using a data cut-off of 20th March 2013 (median follow-up at data cut-off was 878 days). No interim analyses were planned or performed, and the manufacturer has confirmed that no cut-offs later than 20th March 2013 regarding efficacy outcomes have since been performed. As stated in Table 13 of the ERG report, a longer follow-up would be preferable.

Pre-planned sensitivity, sub-group and post-hoc analyses were also undertaken. Sensitivity analyses were performed as follows: per protocol (PP) analysis, progression-free survival (PFS) with computed tomography (CT) scan, PFS adjusted for progression proclaimed by the investigator, PFS with worst case comparison and differential censoring, PFS based on common visits, investigator assessed PFS, and event-free survival (EFS). Sub-groups were categorised based upon: gender, age, race, geographical distribution, Rai and Binet staging, Eastern Cooperative Oncology Group (ECOG) performance status, presence of constitutional symptoms, presence of comorbidities, presence of prognostic factors, reasons why a patient was considered inappropriate for fludarabine-containing regimen, and response. Post-hoc analyses were conducted for: demographics by region, baseline characteristics by region, prognostic markers by region, exposure by region, time in study by region, exclusion of subjects not considered fludarabine-inappropriate, creatinine clearance at screening. The ERG considers these to be appropriate post-hoc analyses.

The submission stated that secondary efficacy analyses of overall response rate (ORR) and overall survival (OS) would only be conducted if the primary endpoint was significant (to control the type I error rate). This is considered appropriate, as is the general statistical approach for secondary efficacy analyses.

Single-arm Study OMB115991

The primary analysis in this single-arm trial was performed on all enrolled participants, apart from one participant with missing data, using a data cut-off of 28th February 2013. Median duration on the study was approximately 8.5 months. A follow-up period of 36 months post-treatment is currently underway but follow-up data are not available. The manufacturer provides ORRs with 95% exact binomial confidence intervals, and also provides the proportion of participants suspected of achieving a primary endpoint of complete response (CR) who were minimal residual disease (MRD) positive. The ERG considers this to be suitable.

See Section 4 of the ERG report for additional information on clinical effectiveness analysis.

Cost-effectiveness

Summary of the Manufacturer's Submitted Evaluation

Model Structure

The submission includes a cohort model and uses the area under the curve (AUC) method for estimating transition probabilities. A diagrammatic representation of the model is given in Figure 23 of the ERG report.

Patients begin in a starting state of untreated chronic lymphocytic leukaemia for whom fludarabine is not appropriate. These patients receive first-line therapy of either chlorambucil (Clb) or ofatumumab + chlorambucil (OfatClb). From this state, patients move to a state depending upon their response. Patients can have complete response, partial response or stable disease, where there is no response to treatment but they remain progression free; or their disease may progress. Patients who are progression free remain so until they experience disease progression or die.

After progression, patients may receive three further lines of treatment. From any line of treatment patients may progress to the state of progressed disease with best supportive care. For patients who respond to first-line treatment (complete or partial response), there is the option of retreatment in progressed disease, before moving to second line treatment. Retreatment and subsequent lines of treatment only affect costs and not quality-adjusted life years (QALYs).

Patients can die in any state.

The manufacturer also models the possibility of patients who suffer progressive multifocal leukoencephalopathy (PML) as a result of their first-line treatment as a separate health state, due the long term impact of PML. PML was not detected in the COMPLEMENT 1 trial, and the incidence of PML is estimated from other sources.

The proportion of the cohort in each health state is calculated as follows:

- The total proportion alive is set to equal the overall survival curve.
- The proportion in one of the progression free health states (CR, partial response [PR], stable disease [SD]) is set to equal the relevant

progression free survival curve. The total proportion in progression free is the sum of the proportions in each of the progression free health states, weighted by the proportions of patients in each response state.
- The proportion in the progression health state at each cycle is the difference between the proportion alive and the proportion progression free.

Cycles in the model last three months and a half-cycle correction was applied.

See Sections 5 and 6 of the ERG report for additional information on cost-effectiveness analysis.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions

Availability and Nature of Evidence

The Committee concluded that, after modifying the post-progression structure according to the Evidence Review Group's (ERG's) exploratory analyses, the company's economic model was structurally acceptable.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee was concerned that the log-normal distribution used by the company to extrapolate progression-free survival for ofatumumab plus chlorambucil compared with chlorambucil could overestimate the proportion of patients whose disease did not progress after trial follow-up ended. It concluded that using the Weibull distribution, as in the ERG's exploratory analyses, was more appropriate than the log-normal distribution used by the company for estimating long-term progression-free survival in this patient population.

The Committee accepted the clinical inputs in the ERG's exploratory base case for the comparison between ofatumumab plus chlorambucil and rituximab plus chlorambucil, based on the results of the indirect treatment comparison using COMPLEMENT 1 patient characteristics. It did, however, recall that the ERG's adjusted indirect treatment comparison using the CLL11 patient characteristics tended to favour rituximab plus chlorambucil.

Incorporation of Health-related Quality-of-Life Benefits and Utility Values. Have Any Potential Significant and Substantial Health-related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

The Committee concluded that it accepted the pre-progression utility values derived from COMPLEMENT 1 data because the EuroQol Five-Dimension (EQ-5D) is a standardised and validated generic instrument that is widely used and has been validated in many patient populations, as well as being NICE's preferred instrument.

The Committee noted that although there was uncertainty around the most appropriate post-progression utility value, it concluded that was not a key driver of the incremental cost-effectiveness ratio (ICER) and that value used by the company in its base case was acceptable.

The Committee noted that the company's evidence submission stated that all relevant health-related benefits were likely to be included in the quality-adjusted life-year (QALY) calculation.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost Effective?

Not applicable

What Are the Key Drivers of Cost-effectiveness?

The Committee noted that the ERG's base-case exploratory analyses for ofatumumab plus chlorambucil compared with rituximab plus chlorambucil used an adjusted indirect comparison derived from COMPLEMENT 1 patient characteristics. This gave very similar total costs and total QALYs when the ofatumumab patient access scheme (PAS) was incorporated. It recalled that the ERG's exploratory sensitivity analyses that used CLL11 patient characteristics to inform the adjusted indirect treatment comparison showed that ofatumumab plus chlorambucil was dominated by rituximab plus chlorambucil when the ofatumumab PAS price was used (that is, it was more expensive and less effective).

Most Likely Cost-effectiveness Estimate (Given as an ICER)

The Committee concluded that the ERG's exploratory base-case ICER of £26,000 per QALY gained, which incorporated the ofatumumab PAS, was the most plausible for ofatumumab plus chlorambucil compared with chlorambucil alone.

The Committee concluded that, when using the ofatumumab PAS price, the cost-effectiveness of ofatumumab plus chlorambucil is likely to be similar to rituximab plus chlorambucil because of small differences in costs and QALYs.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, assessment report and the appraisal consultation

document (ACD) and were provided with the opportunity to appeal against the final appraisal determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered clinical and cost-effectiveness evidence submitted by the manufacturer of ofatumumab and a review of this submission by the Evidence Review Group (ERG). The main clinical effectiveness evidence came from one randomised controlled trial (RCT) and one non-randomised study. For cost-effectiveness, the Appraisal Committee considered an economic model submitted by the manufacturer.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia

Potential Harms

The summary of product characteristics lists the following adverse reactions for ofatumumab, alone or with an alkylating agent, as affecting more than 10% of patients: upper and lower respiratory tract infections, neutropenia, anaemia, nausea, rash and pyrexia.

For full details of adverse reactions and contraindications, see the summary of product characteristics.

Contraindications

Contraindications

For full details of adverse reactions and contraindications, see the summary of product characteristics.

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Care Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate

unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- Section 7(6) of the National Institute for Health and Care Excellence (NICE) (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, National Health Services (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.
- When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has chronic lymphocytic leukaemia and the doctor responsible for their care thinks that ofatumumab is the right treatment, it should be available for use, in line with NICE's recommendations.
- The Department of Health and the company have agreed that ofatumumab will be available to the NHS with a patient access scheme which makes ofatumumab available with a discount. The size of the discount is commercial in confidence. At the time of the appraisal, the marketing authorisation holder was GlaxoSmithKline; however, it is now marketed by Novartis. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to the company's commercial operations team on 01276 698717 or commercial.team@novartis.com.
- NICE has developed tools to help organisations put this guidance into practice (listed below) (see also the "Availability of Companion Documents" field).
    - Slides highlighting key messages for local discussion
    - A costing statement explaining the resource impact of this guidance

Implementation Tools

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Jun. 55 p. (Technology appraisal guidance; no. 344).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Jun

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia. Costing statement. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Jun. 1 p. (Technology appraisal guidance; no. 344). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Hoyle M, Huxley N, Coelho H, Lowe J, Cooper C, Crathorne L, Peters J, Rudin C. Ofatumumab in combination with chlorambucil or bendamustine for previously untreated chronic lymphocytic leukaemia: a critique of the submission from GSK. A Single Technology Appraisal. Exeter (UK): Peninsula Technology Assessment Group (PenTAG), University of Exeter; 2014. 237 p. Electronic copies: Available from the NICE Web site .

Patient Resources

The following is available:

- Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Jun. 3 p. (Technology appraisal guidance; no. 344). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download in ePub or eBook formats from the NICE Web site . Also available in Welsh from the NICE Web site .

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